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Attorney: MARSHALL J. CHICK

Dated: October 22, 2007

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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Appln No.	:	10/600,266
Confirm. No.	:	7488
Applicant(s)	:	Fumitoshi ASAI et al
Filed	:	June 20, 2003
For	:	MEDICINAL COMPOSITIONS CONTAINING ASPIRIN
Art Unit	:	1614
Examiner	:	Brian Yong S. Kown
Docket No.	:	03337C/HG
Customer No.	:	01933

SUPPLEMENTAL AMENDMENT

COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, VA 22313-1450

S I R :

This is to supplement the amendment filed October 16, 2007 in which a Declaration of Dr. Fumitoshi Asai was attached. The Declaration was a Declaration Under 37 CFR 1.131 to predate a reference. To complete the record there is enclosed herewith a substantially identical Declaration which is signed by the other three co-inventors.

Respectfully submitted,

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MJC/sg

MARSHALL J. CHICK
Reg. No. 26,853

Enc. Declaration with attachments

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Appl. No. : 10/600,266

Confirm. No.: 7488

Applicant(s): Fumitoshi ASAI et al

Filed : June 20, 2003

Art Unit : 1614

Examiner : Brian Yong S. Kown

Docket No. : 03337C/HG

For : MEDICINAL COMPOSITIONS CONTAINING ASPIRIN

Customer No.: 01933

DECLARATION UNDER 37 CFR 1.131

The below named declarants hereby declare the following:

1. They are each a co-inventor of the invention described and claimed in the above-identified application.

2. Attached hereto are copies of notebook records documenting experiments done by us (the inventors) or under our supervision and control, showing a reduction to practice of the claimed invention. The code "CS 747" which appears throughout the notebook pages is our internal code for the compound identified as "Compound A" in Table I of the specification of our patent application. The dates on the copies have been blacked out. Translations of these documents are also attached. The acts described in these documents occurred prior to November 3, 1999.

We hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001, of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Date: 10/22/2007 Atsuhiro SUGIDACHI

Date: 10/22/2007 Takatoshi OGAWA

Date: 10/19/2007 Teruhiko INOUE

Attachment: Notebook records and
English translation thereof

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[redacted]

CS 747
+
Aspirin

Combination Experiment

Dose	CS 747	0.3 mg/kg (4hr)	about 40 mg
		1 mg/kg (4hr)	about 20

Dose in which both bleeding time and aggregation were measured:

Aspirin 10 + CS 747 0.6 2hr

First, experiment with a central focus on Aspirin 10 + CS 747 0.6

Another group 0.3 or 1

Conduct 0.3 because 1 seems to work too much.

[redacted]

[redacted]

Arterio-venous Shunt Thrombosis Model in Rats
(Examination of effect by combination of CS-747 with aspirin)

[Object]
Examine the effect by combination of CS-747 with aspirin using Arterio-venous shunt thrombosis model in rats.

[Experimental Term]
Thirty six rats received on [redacted] are used.

[Animals]
Seven-week-old male SD rats (Japan SLC) are purchased and used for the experiment after preliminary breeding for about a week. The experiment is conducted as 6 rats per group.

[Test agents]
CS-747 (synthesized by Ube Industrials Ltd., Lot No. 16) and aspirin (Sigma, A-5376, Lot No. 46H1053, received on [redacted]) are used. The test agents are dissolved or suspended in a 5% Arabic gum (Sigma, Lot No. 73H0705, opened on [redacted]) solution and administered orally in volume of 1 ml/kg two hours before starting arterio-venous shunt. Administered group are (A) vehicle, (B) aspirin 10 mg/kg, (C) CS-747 0.3 mg/kg, (D) CS-747 0.6 mg/kg, (E) aspirin 10 mg/kg + CS-747 0.3 mg/kg, and (F) aspirin 10 mg/kg + CS-747 0.6 mg/kg.

[Methods]
(1) For the experiment, the method by Umetsu et al. (Thromb. Haemost. 39, 74-83, 1978) is partly modified.

(2) The shunt tube for arterio-venous shunt is prepared as follows; both sides of a medical silicon tube of 12 cm length (inner diameter: 1.5 mm, outer diameter: 2.5 mm, KANEKA Medix Co., Ltd) are connected each to a polyethylene tube of 7 cm length (inner diameter: 0.5 mm, outer diameter: 1.0 mm, Natsume Seisakusho Co., Ltd.)

covered with silicon via a medical silicon tube of 0.7 cm length (inner diameter: 1.0 mm, outer diameter: 1.5 mm, KANEKA Medix Co., Ltd.) as connector. At the connection,

[redacted]

surgical adhesive (Aronalpha A, Sankyo) is used for preventing blood leak. In addition, a silk thread (size 3-0, Nicchо Kogyo) of 10 cm length is placed in the tube of 12 cm length.

(3) Vehicle (5% Arabic gum solution) or test agents are administered orally in a volume of 1 ml/kg 2 hours before starting arterio-venous shunt. 6 rats per group are used.

(4) The above tube prepared in advance is filled with heparin solution (Japanese Pharmacopoeia Heparin Sodium Injection, Fuso Pharmaceutical Industries, Ltd., Lot No. 97H28A, received on [redacted]) diluted with normal saline (Otsuka) resulting in 30 unit/kg.

(5) The rat is anesthetized with an intraperitoneal injection of 1 ml/kg (40 mg/kg) of pentobarbital solution (Nembutal R, Abbott, Lot No. 20-975-Z7) diluted with normal saline resulting in 40 mg/ml. After it is fixed to turning up, the jugular vein is exposed and one side of the shunt tube (in which the silk thread is not adhered) is cannulated. Subsequently, to the carotid artery where bloodstream is shut using clamp, the other side of the tube is cannulated to make the arterio-venous shunt.

(6) After removing the clamp and allowing blood to circulate for 30 minutes, the thrombus adsorbed on the silk thread is weighed. The thrombus weight was calculated by subtracting of the weight of the thread (6.5 mg) from the measured weight.

Files were stored at AV-shunt (3) (F00515 data)

[redacted] A. Sugidachi

[redacted]

AV shunt Thrombosis Model in Rats
(Combination of CS 747 with aspirin)

Protocol: P. 146, 147 Reagent and so on: p. 110, p. 138

Cage number: 6raC3-01-04

Rats
SD male (Japan SLC)
[redacted] wks, Receipt
Receipt number: 034163
Sugidachi

Sex, system: male SD
Yearround old: 7 weeks
Body weight:
Manufacture name: Japan SLC
Receive date: [redacted] Number of rats: 36
Experimenter: Atsuhiro Sugidachi
Housing term: [redacted] to [redacted]
Receipt number: 034163

5% Arabic gum soln.
67.7mg aspirin 50 mg/ml = 1011.7 mg / 20.234 ml dH_2O
16.2 mg CS 747

Aspirin
10 mg/ml = 57.7 mg / 5.77 ml 5% Arabic gum soln.
1011.7 mg Arabic gum

CS 747
16.2 mg / 5.4 ml = 3 mg/ml
3 mg/ml soln. 1 ml + 5% Arabic gum soln. 2 ml = 1 mg/ml
1 mg/ml soln. 1 ml + 5% Arabic gum soln. 2.33 ml = 0.3 mg/ml
1 mg/ml soln. 1.5 ml + 5% Arabic gum soln. 1 ml = 0.6 mg/ml
10.7 mg CS 747 Further prepared because of insufficient (spilled)
5% Arabic gum 1084.7 mg / 21.69 ml dH_2O = 50 mg/ml
1084.7 mg Arabic gum CS 747 10.7 mg / 10.7 ml Arabic gum soln. = 1 mg/ml
1 mg/ml soln. 1.5 ml + 5% Arabic gum soln. 3.5 ml = 0.3 mg/ml
1 mg/ml soln. 3 ml + 5% Arabic gum soln. 2 ml = 0.6 mg/ml

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[redacted]

	B. W. (g)	Treatment	Measured value (mg)	Thrombus (mg)
#1	253	Vehicle	61.3	54.8
2	252	Aspirin 10	51.3	44.8
3	262	CS 747 0.3	58.3	51.8
4	267	CS 747 0.6	43.1	36.6
5	256	Aspirin 10 + CS 747 0.3	39.6	33.1
6	271	Aspirin 10 + CS 747 0.6	23.2	16.7
7	250	V	63.2	56.7
8	246	A 10	58.4	51.9
9	258	747 0.3	51.8	45.3
10	269	747 0.6	53.1	46.6
11	268	A 10 + 747 0.3	30.5	24.0
12	244	A 10 + 747 0.6	41.3	34.8
13	247	V	56.1	49.6
14	262	A 10	48.6	42.1
15	256	747 0.3	52.2	45.7
16	267	747 0.6	46.3	39.8
17	268	A 10 + 747 0.3	42.2	35.7
18	242	A 10 + 747 0.6	21.6	15.1

V = Vehicle

A = Aspirin

747 = CS 747

[redacted]

#1
252.9 g
251.7 g
262.3 g
267.3 g
256.4 g
271.1 g

#7
250.0 g
245.8 g
257.8 g
269.0 g
268.3 g
244.4 g

#13
247.0 g
262.3 g
256.2 g
267.3 g
267.6 g
242.1 g

heparin

1000 u/ml soln. 1 ml + saline 9 ml = 100 unit/ml

100 u/ml soln. 3 ml + saline 7 ml = 30 unit/ml

[redacted]

#1	0.0613 g	#7	0.0632 g	#13	0.0561 g
#2	0.0513 g	#8	0.0584g	#14	48.6 mg
#3	0.0583 g	#9	0.0518 g	#15	52.2 mg
#4	0.0431 g	#10	0.0531 g	#16	0.0463 g
#5	0.0396 g	#11	0.0305 g	#17	0.0422 g
#6	0.0232 g	#12	41.3 mg	#18	0.0216 g

[redacted] A. Sugidachi

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[redacted]

AV Shunt Thrombosis Model in Rats
(Aspirin + CS 747)

Protocol: p. 146, 147 Reagents and so on: p. 110, 138

Cage number:	6raC3-01-01			Rat
			6	SD male (7 wks, Receipt)
Sex, system:	male	SD	36+2	Japan SLC
Year-round old:		7 weeks		[redacted] Receipt
Body weight:				Sugidachi
Manufacture name:		Japan SLC		Receipt number: 034163
Receive date:	[redacted]		Number of rats:	36
Experimenter:	Atsuhiro Sugidachi			
Housing term:	[redacted]	to [redacted]		
Receipt number:		034163		

Additional 2 rats
↓
euthanasia using CO_2 gas

[redacted]	B. W.	
#1	271.0 g	72.0 mg
	277.6 g	11.3 mg
	272.8 g	
	276.0 g	
	245.5 g	
#6	261.6 g	1224.1 mg
#10	248.2 g	
#8	263.9 g	
#9	253.3 g	
#7	281.1 g	
#11	263.4 g	
#12	263.4 g	
#13	271.3 g	
	265.3 g	
	266.0 g	
	255.5 g	
	245.6 g	
#16	272.4 g	

5% Arabic gum = 50 mg/ml
= 1224.1 / 24.48 ml dH_2O

Aspirin
10 mg/ml = 72.0 / 7.2 ml 5% Arabic gum soln.

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[redacted]

CS 747 11.3 mg / 11.3 ml 5% Arabic gum soln. = 1 mg/ml
1 mg/ml soln. 1.5 ml + 5% Arabic gum soln. 1ml = 0.6 mg/ml
1 mg/ml soln. 1 ml + 5% Arabic gum soln. 2.33 ml = 0.3 mg/ml

heparin 1000 unit/ml soln. (origine) 1 ml + saline 9 ml = 100 unit/ml
100 unit/ml soln. 3 ml + saline 7 ml = 30 unit/ml

	B. W. (g)	Treatment	Measured value (mg)	Thrombus (mg)
#1	271	V	55.6	49.1
2	278	A 10	52.9	46.4
3	273	747 0.3	43.9	37.4
4	275	747 0.6	41.0	34.5
5	246	A 10 + 747 0.3	24.8	18.1
6	252	A 10 + 747 0.6	19.7	13.2
7	281	V	59.0	52.5
8	264	A 10	63.2	56.7
9	253	747 0.3	47.1	40.6
10	248	747 0.6	38.5	32.0
11	263	A 10 + 747 0.3	36.7	30.2
12	263	A 10 + 747 0.6	35.6	29.1
13	271	V	57.8	51.3
14	265	A 10	44.3	37.8
15	266	747 0.3	46.4	39.9
16	256	747 0.6	42.2	35.7
17	246	A 10 + 747 0.3	48.3	41.8
18	272	A 10 + 747 0.6	36.6	30.1

V = Vehicle
A = Aspirin
747 = CS 747

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[redacted]

#1	0.0556 g	#7	0.0590 g	#13	0.0578 g
#2	0.0529 g	#8	0.0632 g	#14	44.3 mg
#3	0.0439 g	#9	0.0471 g	#15	0.0464 g
#4	0.0410 g	#10	0.0385 g	#16	42.2 mg
#5	0.0246 g	#11	0.0367 g	#17	48.3 mg
#6	0.0197 g	#12	0.0356 g	#18	36.6 mg

[redacted] A. Sugidachi Hirose [redacted]

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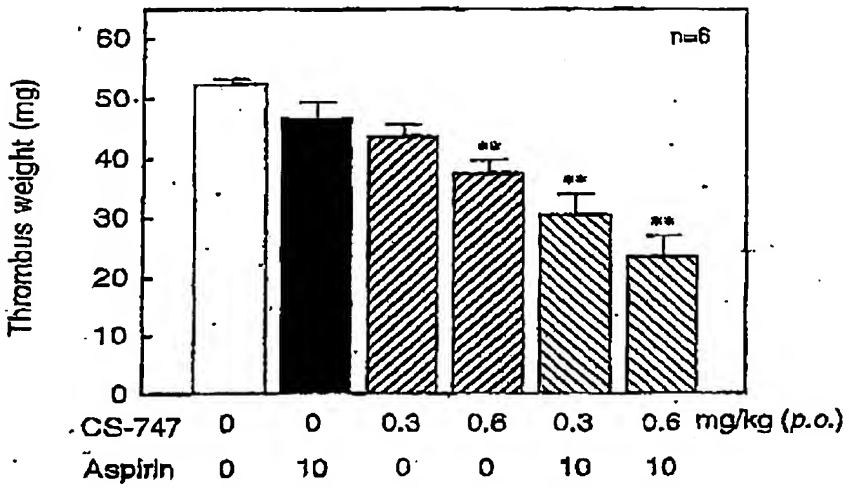
[redacted]

Arterio-venous shunt thrombosis model in rats



Aspirin + CS 747 Summary

Vehicle	52.3 ± 1.2
Aspirin [10]	46.6 ± 2.8
CS 747 [0.3]	43.5 ± 2.1
CS 747 [0.6]	37.5 ± 2.1
Aspirin [10] + CS 747 [0.3]	30.5 ± 3.5
Aspirin [10] + CS 747 [0.6]	23.2 ± 3.8

[redacted] A. Sugidachi

[redacted] [redacted]

CS747 + Aspirin) 併用 Exp. 行なう.

Dose CS747 0.3 mg/kg (4hr) で 約40 mg.
1 mg/kg (4hr) で 約20

出血時間, 凝集 とも 行っている dose は
Aspirin ⑩ + CS747 (0.6) 2hr

まず Aspirin ⑩ + CS747 (0.6) を中心として行なう。
CS 747 (0.3) ～ ① ～①は多分効きすぎるので (0.3) と行なう。

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[redacted]
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CS-
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No.
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(2)
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147

[redacted]

ラット

ロンアルファA、三共）で接着する。また12 cmのチューブ内に10 cmの絹糸（3-0、日腸工業）を設置する。

(3) 動静脈シャント開始2時間前に、vehicle（5%アラビアゴム溶液）または薬物を1 ml/kgの割合で経口投与する。1群6匹の実験を行う。

(4) あらかじめ作成しておいた上記チューブに30 unit/kgとなるように、生理食塩液（大塚）で希釈したヘパリン溶液（日本薬局方ヘパリンナトリウム注射液、扶桑薬品工業、Lot No. 97H28A、[redacted]入荷）を満たす。

(5) 生理食塩液で40 mg/mlに希釈したペントバルビタール溶液（ネンブタール®、Abbott、Lot No. 20-975-Z7）を1 ml/kg腹腔内投与（40 mg/kg）してラットを麻酔させる。仰臥位に固定させた後、頸静脈を露出させ、シャント用チューブの片側（糸の付いていない方）をカニュレーションする。続いて、クレンメで血流を遮断しておいた頸動脈に、チューブの反対端をカニュレーションし、動静脈シャントを形成する。

(6) クレンメをはずしてシャントに30分間血液を循環させた後、絹糸に付着した血栓の湿重量を測定する。測定重量から糸の重量（6.5 mg）を差し引き血栓重量を求める。

ケージ
性別、
周
3 薬入実
飼育
受付

57.
16.
1011.

ファイル AV-shunt(ラ) に保存.
(E00515データ)

19.7
1084.7

[redacted] A. Sugitani

149

[redacted]

	B.W.(g)	Treatment	測定値(mg)	Thrombus(mg)
#1	253	Vehicle	61.3	54.8
2	252	Aspirin (10)	51.3	44.8
3	262	CS747 (0.3)	58.3	51.8
4	267	CS747 (0.6)	43.1	36.6
5	256	Aspirin (10) + CS747 (0.3)	39.6	33.1
6	271	Aspirin (10) + CS747 (0.6)	23.2	16.7
7	250	V	63.2	56.7
8	246	A (10)	58.4	51.9
9	258	747 (0.3)	51.8	45.3
10	269	747 (0.6)	53.1	46.6
11	268	A (10) + 747 (0.3)	30.5	24.0
12	244	A (10) + 747 (0.6)	41.3	34.8
13	247	V	56.1	49.6
14	262	A (10)	48.6	42.1
15	256	747 (0.3)	52.2	45.7
16	267	747 (0.6)	46.3	39.8
17	268	A (10) + 747 (0.3)	42.2	35.7
18	242	A (10) + 747 (0.6)	21.6	15.1

[redacted]

#1 252.9g
251.7g
262.3g
267.3g
256.4g
271.1g

#7 250.8g
245.8g
257.8g
269.0g
268.3g
244.4g

#13 247.8g
262.3g
256.2g
267.3g
267.6g
242.1g

V = Vehicle
A = Aspirin
747 = CS 1747

ヘパリン
1000 u/ml soln. 1ml + saline 9ml = 100 unit/ml
100 u/ml soln. 3ml + saline 7ml = 30 unit/ml

#1 B.
#2 B.
#3 B.
#4 B.
#5 B.
#6 B.

151

[redacted]

ラット AV shunt 血栓モデル
(アスピリン + CS747)

プロトコール p146, 147 試薬 p110, 138

ケージ番号: 67C3-01-01
性別、系統: ♂ SD
週年令: 7週
体重:
業者名: 日本SLC
入荷日: [redacted]
実験者: 杉立 取寛
飼育期間: [redacted]~[redacted]
受付番号: 034163

6
36+2
匹数: 36

ラット
SD ♂ (7wks 入荷)
日本SLC
[redacted] 入荷
杉立
受付番号 034163

おまけ2匹
↓
CO_2 gas で安楽死
させた。

[redacted] B.w.

#1 271.8g
277.6g
272.8g
275.6g
245.5g
#6 251.6g

#10 248.2g
#8 263.9g
#9 253.3g
#7 281.1g
#11 263.4g
#12 263.4g

#13 271.3g
265.3g
266.0g
255.5g
245.6g
#18 272.4g

72.0 mg
11.3 mg

1224.1 mg

5% アラビアゴム = 50 mg/ml
= 1224.1 / 24.48 ml dH_2O

・Aspirin
10 mg/ml = 72.0 / 7.2 ml 5% アラビアゴム soln.

CS74

ヘパ

	B.w.
#1	271
2	278
3	273
4	275
5	246
6	252
7	281
8	264
9	253
10	248
11	263
12	263
13	271
14	265
15	266
16	256
17	246
18	272

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[redacted]

#1 0.0556 g
#2 0.0529 g
#3 0.0439 g
#4 0.0410 g
#5 0.0246 g
#6 0.0197 g
#7 0.0590 g
#8 0.0632 g
#9 0.0471 g
#10 0.0385 g
#11 0.0367 g
#12 0.0356 g
#13 0.0578 g
#14 44.3 mg
#15 0.0464 g
#16 42.2 mg
#17 48.3 mg
#18 36.6 mg

Thrombin weight (—)

Aspirin + C

Vel
A
C
CS
A
A

[redacted] A. Sugiyama